Kidney International, Vol. 57 (2000), pp. 1412–1417

Glucocorticoids, 11β-hydroxysteroid dehydrogenase, and fetal programming

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Glucocorticoids, 11β-hydroxysteroid dehydrogenase, and fetal programming. Epidemiological studies in many distinct human populations have associated low weight or thinness at birth with a substantially increased risk of cardiovascular and metabolic disorders, including hypertension and insulin resistance/type 2 diabetes, in adult life. The concept of fetal "programming" has been advanced to explain this phenomenon. Prenatal glucocorticoid therapy reduces birthweight, and steroids are known to exert long-term organizational effects during specific "windows" of development. Therefore, we hypothesized that fetal overexposure to endogenous glucocorticoids might underpin the link between early life events and later disease. In rats, birthweight is reduced following prenatal exposure to the synthetic glucocorticoid dexamethasone, which readily crosses the placenta, or to carbenoxolone, which inhibits 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), the physiological feto-placental "barrier" to endogenous glucocorticoids. Although the offspring regain the weight deficit by weaning, as adults they exhibit permanent hypertension, hyperglycemia, and increased hypothalamic-pituitary-adrenal axis activity. Moreover, physiological variations in placental 11β-HSD2 activity near term correlate directly with fetal weight. In humans, 11β-HSD2 gene mutations produce a low birthweight, and some studies show reduced placental 11β-HSD2 activity in association with intrauterine growth retardation. Moreover, low birthweight babies have higher plasma cortisol levels throughout adult life, indicating that hypothalamic-pituitary-adrenal axis programming also occurs in humans. The molecular mechanisms of glucocorticoid programming are beginning to be unraveled and involve permanent and tissue-specific changes in the expression of key genes, notably of the glucocorticoid receptor itself. Thus, glucocorticoid programming may explain, in part, the association between fetal events and subsequent disorders in adult life.

Extensive epidemiological studies suggest that factors operating in early life are important determinants of the risk of common and interassociated cardiovascular and metabolic disorders of adult life. Data from several distinct populations in the Europe, Asia, Australia, and North America have shown that low birthweight or thinness at birth strongly predicts the subsequent occurrence of hypertension, hyperlipidemia, insulin resistance, type 2 diabetes, and ischemic heart disease deaths in adult life [1–13]. Classic adult lifestyle risk factors (smoking, alcohol, obesity, social class) appear to be additive to these early life effects [3]. Importantly, the relationships represent birthweights within the normal range, rather than severe intrauterine growth retardation, multiple babies, or very premature babies. Indeed, the smaller of twins at birth apparently has the higher blood pressure in later life [14]. Postnatal "catch-up" growth is also a risk factor for subsequent hypertension, ischemic heart disease, and insulin resistance [3, 9, 14, 15], perhaps suggesting that smallness at birth due to environmental influences restraining intrauterine growth are of importance. The "early life" associations appear also to be important predictors of later disease. In Preston, a small baby with a large placenta had a relative risk of adult hypertension three times that of a large baby with a normal placenta [16]. In 22,000 American men, babies born lighter than 5.5 pounds had a relative risk of adult hypertension of 1.26 and of type 2 diabetes of 1.75 compared with babies of average birthweight. Similarly, the relative risk of hypertension in light normal babies was 1.43 in 71,000 female U.S. nurses [5, 6].

PROGRAMMING

To explain these findings, the concept of early life physiological "programming" has been proposed [3, 17, 18]. Such programming has been shown in a variety of experimental model systems and reflects the action of a factor during a sensitive period or "window" of development to exert organizational effects that persist through life. Perinatally, programming factors might produce adaptations that optimize survival under conditions of stress or deprivation; such responses might be detrimental when the adult environment is not as adverse as "anticipated." Of course, genetic and epigenetic factors that restrain fetal growth and produce later disease may also explain these phenomena, and indeed, loci linked to both low birthweight and adult disorders have been

Key words: placenta, fetal growth, glucocorticoid receptor, type 2 diabetes mellitus, hypertension.

reported [19, 20]. However, the data suggest that environmental effects occur, and these have been the main focus of mechanistic research.

A major environmental factor advocated in explanation of fetal programming is maternal malnutrition. Indeed, dietary restriction during pregnancy in rats, particularly of protein, produces some reduction in birthweight and permanent hypertension and hyperglycemia in the adult offspring [21–24], effects amplified by later obesity. However, the mechanisms that mediate the effects of maternal undernutrition on later disease in the offspring are not fully understood, and any relevance in modern human populations is moot [25]. Even studies of people born during the extreme starvation of the siege of Leningrad in World War II do not support any strong association between maternal nutrition and offspring disorders [26].

GLUCOCORTICOIDS AND PROGRAMMING

Long-term organizational effects are typically found with hormones, particularly steroids. An example is the action of androgens, which neonatally program the expression hepatic steroid-metabolizing enzymes, the development of sexually dimorphic structures in the brain and of sexual behavior [27, 28]. These effects can only be exerted during a specific perinatal period, but then persist throughout life, largely irrespective of any subsequent sex steroid manipulations.

Physiological glucocorticoids (cortisol in humans, corticosterone in rats and mice) are synthesized in the adrenal cortex. Several features of fetal glucocorticoid overexposure suggest a plausible role in the early life programming of adult cardiovascular and metabolic disorders.

Exogenous glucocorticoids retard fetal growth in humans and experimental animals, including nonhuman primates [18, 29–32]. In humans, fetal cortisol levels are increased in intrauterine growth retardation, whether idiopathic or caused by pre-eclampsia [33, 34].

Prenatal glucocorticoids alter the rate of maturation of various organs such as the lung, heart, kidney, and gut [reviewed in 18]. Some effects are transient, whereas others persist throughout life. Perinatal glucocorticoids or stress program specific effects in the brain, notably the hypothalamic-pituitary-adrenal (HPA) axis and dopaminergic motor systems [35–40]. Glucocorticoids also program the immune system [41] and the kidney [42, 43].

Glucocorticoid receptors (GRs) are highly expressed in most, if not all, fetal tissues from midgestation or earlier [44, 45], as well as in placenta and fetal membranes.

Glucocorticoids increase blood pressure and blood glucose levels in adults [46]. Cortisol also elevates fetal blood pressure when infused directly in utero in sheep [47] and at birth in humans and sheep [32, 48].

GLUCOCORTICOID PROGRAMMING

Crucially, prenatal glucocorticoid exposure produces permanently elevated offspring blood pressure levels in later life. Treatment of pregnant rats with modest doses of dexamethasone, a synthetic glucocorticoid used in obstetric practice, reduces birthweight and elevates blood pressure in the adult offspring [49]. Even short-term glucocorticoid exposure in the last trimester increases blood pressure in adult life in rats [50]. These effects are not related to persisting differences in offspring weight, which normalizes by weaning. Last-trimester administration of dexamethasone also "programs" permanent hyperglycemia and, particularly, hyperinsulinemia in the adult offspring [51]. In contrast, earlier prenatal or postnatal exposure to dexamethasone, while reducing fetal or infant growth, has no persisting effects on glucose homeostasis in adult life.

PHYSIOLOGICAL GLUCOCORTICOIDS AND PLACENTAL 11β-HYDROXYSTEROID DEHYDROGENASE TYPE 2

Although glucocorticoids are highly lipophilic and rapidly cross the placenta, normally the fetus has much lower levels of physiological glucocorticoids than its mother [52, 53]. This is achieved by placental 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2), which catalyzes the rapid metabolism of cortisol and corticosterone to inert 11-keto forms (cortisone, 11-dehydrocorticosterone) [54, 55]. This placental enzymic barrier ensures that most, but not all [56], maternal cortisol is inactivated so that the majority of cortisol in the human fetal circulation at term is derived from the fetal adrenals. Dexamethasone, a poor substrate for 11β-HSD2, crosses the placenta readily. The efficiency of placental 11β-HSD2 near term varies considerably in both rats and humans [49, 57]. It has therefore been hypothesized that relative deficiency of placental 11β-HSD2, by allowing increased access of maternal glucocorticoids to the fetus, may retard growth and program responses leading to later disease (Fig. 1) [17]. Indeed, in rats, lower placental 11β-HSD activity and presumably greater fetal exposure to maternal glucocorticoids are seen in the smallest fetuses with the largest placentas. Similar associations between birthweight and placental 11β-HSD2 have been mooted in humans [57], although not all studies have confirmed this observation [58]. However, deleterious mutations of the 11β-HSD2 gene in humans associate with very low birthweight [59]. Furthermore, biochemical markers of fetal exposure to glucocorticoids correlate with placental 11β-HSD2 function at term [60]. Mechanistic studies in pregnant rats with the 11β-HSD carbenoxolone have shown similar effects to dexamethasone, with reduced birthweight and hypertension and hyperglycemia in the adult offspring (Fig. 2) [61, 62]. These effects of carben-

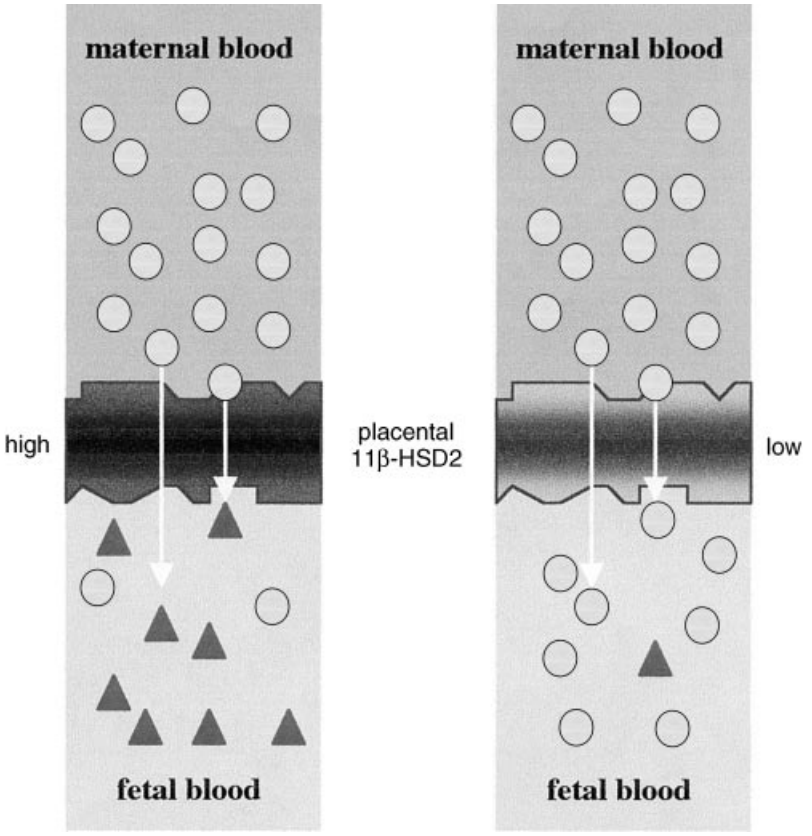

Fig. 1. Placental 11β-hydroxysteroid dehydrogenase type 2 (11β-HSD2) acts as a "barrier" to active glucocorticoids (cortisol, ○) in the maternal circulation, converting these to inert 11 keto forms (cortisone, ▲). Lower activity of placental 11β-HSD2 (right panel) allows greater passage of cortisol to the fetal circulation, which may underlie deleterious short-and long-term effects, including intrauterine growth retardation and "programming" of responses.

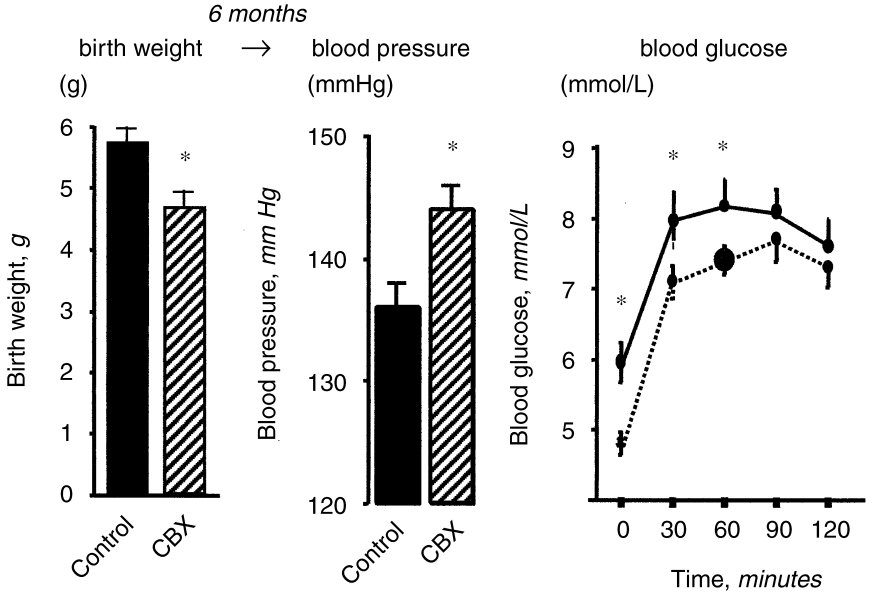

Fig. 2. Prenatal carbenoxolone (CBX) treatment reduces birthweight (▨) and programs permanent hypertension and hyperglycemia (fasting and post-prandial) in the adult offspring compared with control offspring (Con; ■) of vehicle-treated pregnancies. Adult offspring were given oral glucose after 0 minutes. Symbols are: (●, solid line) CBX in utero; (●, dashed line) control.

oxolone are apparently independent of changes in maternal blood pressure or electrolytes, but require maternal glucocorticoids (that is, they are not seen in the offspring of adrenalectomized pregnant rats given carbenoxolone). Intriguingly, dietary protein restriction during rat pregnancy selectively attenuates 11β-HSD2, but not other enzymes in the placenta [63], and leads to hypertension, hyperglycemia, and so forth. Thus, glucocorticoid exposure may be one of a limited series of common mechanisms linking maternal environmental factors with fetal

growth and programming. Indeed, in the maternal protein restriction model, offspring hypertension can be prevented by giving the pregnant dam (and her offspring) glucocorticoid synthesis inhibitors, and can be recreated by concurrent "replacement" of corticosterone, at least in female offspring [64]. A note of caution is necessary, however, since 11β-HSD2 null mice have a normal birthweight [65]. However, in mice, there is early "shut-off" of 11β-HSD-2 gene expression in the placenta during midgestation [66], whereas birthweight predominantly reflects growth late in gestation. Thus, in this species, the "barrier" may not exist during the phase of maximal growth. In contrast, the activity of 11β-HSD2 in rat placenta is maintained until later in gestation [49], and in many other mammals, including humans, placental 11β-HSD2 activity is fully maintained or even increases toward term [57, 67]. Thus, there are clear species differences in the ontogeny of 11β-HSD-2 expression in the placenta, hindering the confidence in extrapolating data from results with 11β-HSD inhibition/disruption in rodent species (particularly the mouse) to humans.

Sites of glucocorticoid action

Glucocorticoids or 11β-HSD inhibitors administered during pregnancy might affect the fetus, the placenta, and/or the mother. Each is plausible [reviewed in 18], although direct feto-placental effects seem most likely [61, 62]. Nevertheless, maternal hypertension is linked to fetal high blood pressure and hyperglycemia [68, 69]. 11β-HSD2 is also highly expressed in many fetal tissues until midgestation in rodents and humans [66, 70], which may provide additional tissue-specific controls of steroid action. Finally, several important placental functions are affected by glucocorticoids, including peptide and steroid biosynthesis and antagonism of progesterone action [71–73], which might affect placental growth.

Tissue mechanisms of fetal programming

Prenatal maternal protein restriction or glucocorticoid exposure affects glucose-insulin homeostasis in the adult offspring. A key target appears to be the liver, where glucocorticoids regulate several important processes, including key enzymes regulating carbohydrate and fat metabolism, such as phosphoenolpyruvate carboxykinase, the rate-limiting step in gluconeogenesis. Prenatal glucocorticoid administration programs increased phosphoenolpyruvate carboxykinase gene transcription selectively in the periportal zone of the liver acinus and hence increased enzyme activity [51]. Recent data suggest that permanently increased hepatic GR expression, again only in the periportal zone, may underpin the programming of elevated hepatic phosphoenolpyruvate carboxykinase and adult hyperglycemia. Indeed, rats exposed to dexamethasone in the last trimester show increased rises in plasma glucose levels on exposure to corticosterone, suggesting the increased hepatic GR expression is of functional importance [51]. Of course, this begs the question of what happens to plasma corticosterone levels in such models.

Prenatal dexamethasone permanently attenuates GR (and mineralocorticoid receptor) gene expression in the adult rat hippocampus, a key region responsible for mediating glucocorticoid negative feedback on the HPA axis. This may well underpin the documented increases in basal plasma corticosterone levels in adulthood by reducing sensitivity to glucocorticoid feedback [50]. Of course, elevated glucocorticoid levels might contribute directly to hypertension and hyperglycemia [49]. The reader will have noted that GR transcript levels are elevated in the liver, but reduced in the hippocampus in the prenatal dexamethasone model. The molecular mechanisms are under current study, but may reflect differential promoter usage by the GR gene in each tissue.

Crucially, the rat models have allowed further predictions to be made in humans. Indeed, low birthweight also correlates with increased adult cortisol levels in humans [74]. Thus, the prenatal glucocorticoid exposure models have reproduced and indeed extended our understanding of the fetal origins phenomena. Whether glucocorticoids and feto-placental 11β-HSD2 deficiency are common or exceptional mechanisms of fetal programming in humans remains a key question for future investigation.

ACKNOWLEDGMENTS

Research in the authors' laboratory is generously supported by a Wellcome Trust Programme grant (J.R.S.), a Wellcome Veterinary Training Fellowship (M.C.), a WHO Training Fellowship (M.J.N.), and project grants from the Wellcome Trust, the Medical Research Council, the Scottish Hospital Endowments Research Trust, and the High Blood Pressure Foundation.

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